nature reviews neurology

https://doi.org/10.1038/s41582-023-00916-w

Review article

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Myasthenia gravis: the changing treatment landscape in the era of molecular therapies

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Abstract

Myasthenia gravis (MG) is an autoimmune disorder that affects the neuromuscular junction, leading to muscle weakness and fatigue. MG is caused by antibodies against the acetylcholine receptor (AChR), the muscle-specific kinase (MuSK) or other AChR-related proteins that are expressed in the postsynaptic muscle membrane. The standard therapeutic approach for MG has relied on acetylcholinesterase inhibitors, corticosteroids and immunosuppressants, which have shown good efficacy in improving MG-related symptoms in most people with the disease; however, these therapies can carry a considerable burden of long-term adverse effects. Moreover, up to 15% of individuals with MG exhibit limited or no response to these standard therapies. The emergence of molecular therapies, including monoclonal antibodies, B cell-depleting agents and chimeric antigen receptor T cell-based therapies, has the potential to revolutionize the MG treatment landscape. This Review provides a comprehensive overview of the progress achieved in molecular therapies for MG associated with AChR antibodies and MuSK antibodies, elucidating both the challenges and the opportunities these therapies present to the field. The latest developments in MG treatment are described, exploring the potential for personalized medicine approaches.

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Introduction

Myasthenia gravis (MG) is a chronic autoimmune disorder of the neuromuscular junction. The clinical hallmark of MG is muscle weakness associated with fatigability, which can lead to potentially life-threatening exacerbations, such as myasthenic crisis characterized by respiratory failure necessitating intubation[1]. Muscle weakness in MG differs between individual muscles and muscle groups. In ocular MG, only the extraocular muscles are affected, resulting in eyelid ptosis and diplopia. Individuals with generalized MG show a broader spectrum of muscle weakness and fatigability, affecting the cranial nerve-innervated 'bulbar' muscles, the limbs and the neck[2].

MG is caused by IgG antibodies binding to the extracellular domains of antigens that are expressed on the motor endplate of the neuromuscular junction. IgG specific to the muscle nicotinic acetylcholine receptor (AChR) are detected in around 80–85% of people with MG; a smaller subset of individuals (4–8%) have IgG antibodies specific to the muscle-specific kinase (MuSK) protein[2]. In addition, antibodies specific to lipoprotein receptor protein 4 (LRP4) have been identified in some individuals; however, determining the prevalence of these antibodies has been challenging owing to the wide range of reported positivity rates, which vary between 2% and 50%[3–5]. A lack of standardization of LRP4 antibody testing across research laboratories could contribute to these discrepancies. Furthermore, a study in 2022 indicated that commercial cell-based testing for LRP4 IgG antibodies has limited diagnostic use[6].

Historically, the management of MG has predominantly relied on acetylcholinesterase inhibitors (AChE-I), steroids and immunosuppressants to improve symptoms and limit the autoimmune response[7]. These treatment strategies are satisfactory for most individuals with MG; however, extended use of corticosteroids can result in long-term systemic adverse effects including diabetes, hypertension and osteoporosis[8]. Most non-steroidal immunosuppressants have a delayed onset of action, necessitating several months of treatment before their full benefits become apparent[9]. In addition, these medications carry the risk of adverse effects in various organ systems such as the liver and bone marrow[10]. Furthermore, approximately 10–15% of people with MG fail to respond to conventional immunotherapy and are considered to have refractory disease[11]. The advent of molecular therapies has transformed the treatment landscape of MG. These innovative therapies are specifically engineered to target the complement activation, immunoglobulin recycling pathway and immune cells that play a crucial part in the pathogenesis of MG, offering promising tools to improve outcomes for people with the disease.

This Review focuses on the changing treatment landscape of MG associated with AChR (AChR-MG) and MuSK (MuSK-MG) antibodies and delves into the mechanisms of action, efficacy, safety and limitations of the new treatments. The transformative potential of the new therapies in redefining the management of MG and their implications on patient care highlight the importance of implementing personalized treatment strategies that are tailored to the individual needs of those with the disease.

MG pathophysiology: an overview

MG is a heterogeneous disease that encompasses various subtypes characterized by distinct antibodies and immunopathogenic mechanisms (Table 1). The aetiologies and triggers of the different MG subtypes, including early-onset MG, late-onset MG and thymoma-associated MG, remain to be established. However, genome-wide association studies and single-cell technologies offer promising pathways for unravelling the genetic predisposition to MG and the immunobiology of the disease[12–14].

The pathogenesis of MG is a paradigm of a T cell-dependent, B cell-mediated autoimmune response. The immunobiology of MG has been extensively reviewed[15,16] and a summary is provided here (Fig. 1). Anti-AChR and anti-MuSK antibodies generated by B cells undergo class switching and somatic hypermutation, indicative of affinity maturation processes that are supported by interactions with antigen-specific $CD4^+$ T helper (T_H) cells[17]. These autoreactive T cells are activated by antigen-presenting cells exposing major histocompatibility complex (MHC) class II that carry peptide fragments of AChR or MuSK proteins.

B cell development begins in the bone marrow with progenitor B cells that express B cell receptors. These cells advance to pre-B cells, characterized by complete light chain rearrangement and IgM expression, then enter the peripheral circulation as mature B cells. With the aid of $CD4^+$ T cells, the B cells enter a phase of somatic hypermutation and clonal expansion within germinal centres located in secondary lymphoid organs.

The developmental cascade fosters the emergence of high-affinity, class-switched antibodies, as well as the genesis of memory B cells, short-lived plasmablasts that express CD20, and long-lived plasma cells in which CD20 expression is lost[18]. Plasma cells maintain steady-state serum antibody concentrations, whereas memory B cells are primed for a rapid response upon subsequent encounters with the antigen. MuSK antibodies are prominently produced by short-lived plasmablasts, and the phenotype of B cells producing AChR antibodies remains to be established[19]. Clinical observations, such as the different beneficial effects of anti-CD20 treatment in MuSK-MG and AChR-MG, support a distinct immunobiology of the MG subtypes[20].

MG associated with AChR antibodies

People with AChR-MG can exhibit varying degrees of weakness in the extraocular, bulbar, limb and axial muscles. Around 60% of individuals experience symptoms such as ptosis or diplopia, or a combination of both, although the disease is confined to the extraocular muscles in approximately 20% of people[21]. Weakness in the external eye muscles is most often asymmetrical, whereas limb weakness is symmetrical and predominantly affects proximal muscles more than distal ones[2]. The diversity in symptom presentation can be attributed to a complex interplay of factors influencing neuromuscular transmission, the affinity and avidity of antibodies and the regenerative capacity of the motor endplate[2,22,23].

AChR-MG is classified into early-onset MG, typically manifesting before the age of 50 years, late-onset MG, and MG associated with thymoma[24]. Individuals with the early-onset form typically exhibit a hyperplastic thymus that contains germinal centres serving as sites for robust B cell responses against the AChR[25]. This subgroup is more prevalent in women and is associated with the MHC haplotype HLA-B8-DR3-DQ2 (ref. 26). By contrast, the late-onset AChR-MG subgroup mostly comprises individuals who have a normal or atrophic thymus; this form is more common in men and an association with HLA-DRB1*15:01 has been reported[27]. Thymoma occurs in about 20% of individuals with AChR-MG, equally in men and women[28]. Thymoma risk is greatest in individuals whose myasthenic symptoms begin in the fourth to sixth decade of life and is low when myasthenic symptoms begin before 20 years or after 70 years of age[29].

The AChR expressed on the postsynaptic membrane of the neuromuscular junction is a heteropentamer, formed by two α1-subunits and one each of β-subunit, δ-subunit and ε-subunit (adult type) assembled

Table 1 | Clinical and pathological characteristics of the different subtypes of myasthenia gravis

Subgroup	Antibody	Age at onset	Thymus	Clinical manifestations	IgG subclass	Complement activation	Antibody-secreting cell subsets
Early onset	AChR	<50 years	Hyperplasia common	Ocular and limb weakness	IgG1, IgG3	Yes	Short-lived plasmablasts, long-lived plasma cells
Late onset	AChR	>50 years	Atrophy common	Frequent bulbar symptoms	IgG1, IgG3	Yes	Short-lived plasmablasts, long-lived plasma cells
Thymoma	AChR	Any age (most frequent at 40–60 years)	Cortical thymoma (type B) common	Frequent bulbar symptoms	IgG1, IgG3	Yes	Short-lived plasmablasts, long-lived plasma cells
MuSK	MuSK	Any age	Normal	Frequent bulbar symptoms and myasthenic crisis	IgG4	None	Short-lived plasmablasts
LRP4	LRP4	Any age	Normal	Similar to AChR-MG	IgG1	Unknown	Unknown
Seronegative	None detected	Any age	Unknown	Frequent ocular MG	Unknown	Unknown	Unknown

AChR, acetylcholine receptor; LRP4, lipoprotein receptor 4; MG, myasthenia gravis; MuSK, muscle-specific kinase.

around a central pore[30]. In fetal AChR, the ε-subunit is replaced by a γ-subunit. AChR antibodies have pathogenic potential and can bind to multiple subunits; however, a substantial proportion of these antibodies specifically target the α1-subunits[31]. Compelling evidence from an experimental rat model of MG induced by active immunization with the extracellular domain of the AChR α1-subunit supports the crucial role of IgG specific to the α1-subunits in the pathogenesis of MG[32]. This enhanced pathogenic potential can probably be attributed to the α-subunit's localization within the receptor, rendering the subunit more susceptible to antibody binding, as well as its role in modulating the sensitivity of acetylcholine binding[33].

Predominantly belonging to the IgG1 and IgG3 subclasses, AChR antibodies exert their pathogenic effects by three main mechanisms: crosslinking and receptor internalization, receptor blocking, and activation of the complement system[34]. Compelling evidence exists that complement activation has a crucial role in the immunopathogenesis of AChR-MG (Fig. 1), as discussed below[35,36].

The role of complement activation in AChR-MG. The complement system is an essential component of the innate immune response. The system is formed by a cascade of plasma proteins and serves as a functional bridge between innate and adaptive immunity, and is a key effector in the inflammatory response[37]. The complement cascade can be activated through three primary pathways, each representing a distinct sequence of proteolytic events leading to a common terminal sequence: the activation of C3, the central component of the system[38]. The classic pathway is mostly contingent on the binding of IgM, IgG1 or IgG3 to a target antigen and the activation of the C1q complex. The lectin pathway is initiated by mannose-binding lectin or ficolins that recognize specific carbohydrate patterns on microbial surfaces, activating associated serine proteases. Last, the alternative pathway proceeds independently of antibodies, triggered instead by the spontaneous hydrolysis of C3 and its subsequent deposition on pathogen surfaces or binding to properdin. The convergence of these pathways on C3 activation triggers a series of downstream effects, culminating in the activation of the C5 fragment and the formation of the membrane attack complex (MAC), leading to lysis of the membrane of the target cell. Given its potency, the complement system is tightly controlled by a network of regulatory proteins to prevent inadvertent host tissue damage[38].

The involvement of the complement system in MG was initially recognized by the presence of C3 and C9 localized to degenerated junctional folds in the neuromuscular junctions of people with MG and in experimental models of the disease[39,40]. AChR antibodies have an important role in facilitating complement fixation, as demonstrated in animal models through active immunization or passive transfer, which result in complement deposition at the neuromuscular junction and subsequent destruction of the postsynaptic endplate, mirroring the pathological changes observed in humans with MG[36,40].

Additional evidence supporting the role of complement in MG pathogenesis comes from studies involving animals with a genetic deficit of complement components C3, C4, C5 or C6. In these animals, the presence of IgG deposits at the neuromuscular junction does not induce the formation of the MAC, and the incidence of experimental autoimmune MG is markedly reduced compared with that in non-deficient animals[41–43]. Additionally, the administration of inhibitors of the C1q, C5 and C6 components impair MAC formation and alleviate symptoms in experimental autoimmune MG[44–46]. Small interfering RNAs have been used to inhibit the expression of complement components in MG animal models[47]. In particular, suppression of C2 and C5 in mice with experimental autoimmune MG led to a decrease in serum complement activity, resulting in reduced weakness, preserved AChR levels and diminished deposition of MAC[47,48].

Mechanisms of autoantibody production: the role of the thymus. Immunological tolerance is a physiological state in which the immune system is unresponsive to specific antigens, particularly self-antigens. This state is largely established in the thymus, where T cells are programmed for self-tolerance through central tolerance mechanisms. Thymic epithelial cells (TECs), found in both cortical (cTECs) and medullary (mTECs) regions of the thymus, are instrumental in this process. The developing T cells undergo three primary transitional stages. First, T cell receptor gene recombination generates a diverse array of receptors, determining T cell lineage and function. Second, positive selection ensures that T cells with moderate affinity for self-MHC molecules receive survival signals from cTECs. Last, negative selection in the medulla eliminates T cells with high affinity for self-antigens, a process regulated by *AIRE* and *Fezf2* genes, which promote the expression by mTECs of various tissue-restricted antigens, preventing autoimmunity and preserving self-tolerance[49].

The mechanisms underlying the breakdown of self-tolerance and the subsequent selective production of AChR antibodies in MG remain elusive. However, several lines of evidence support a crucial

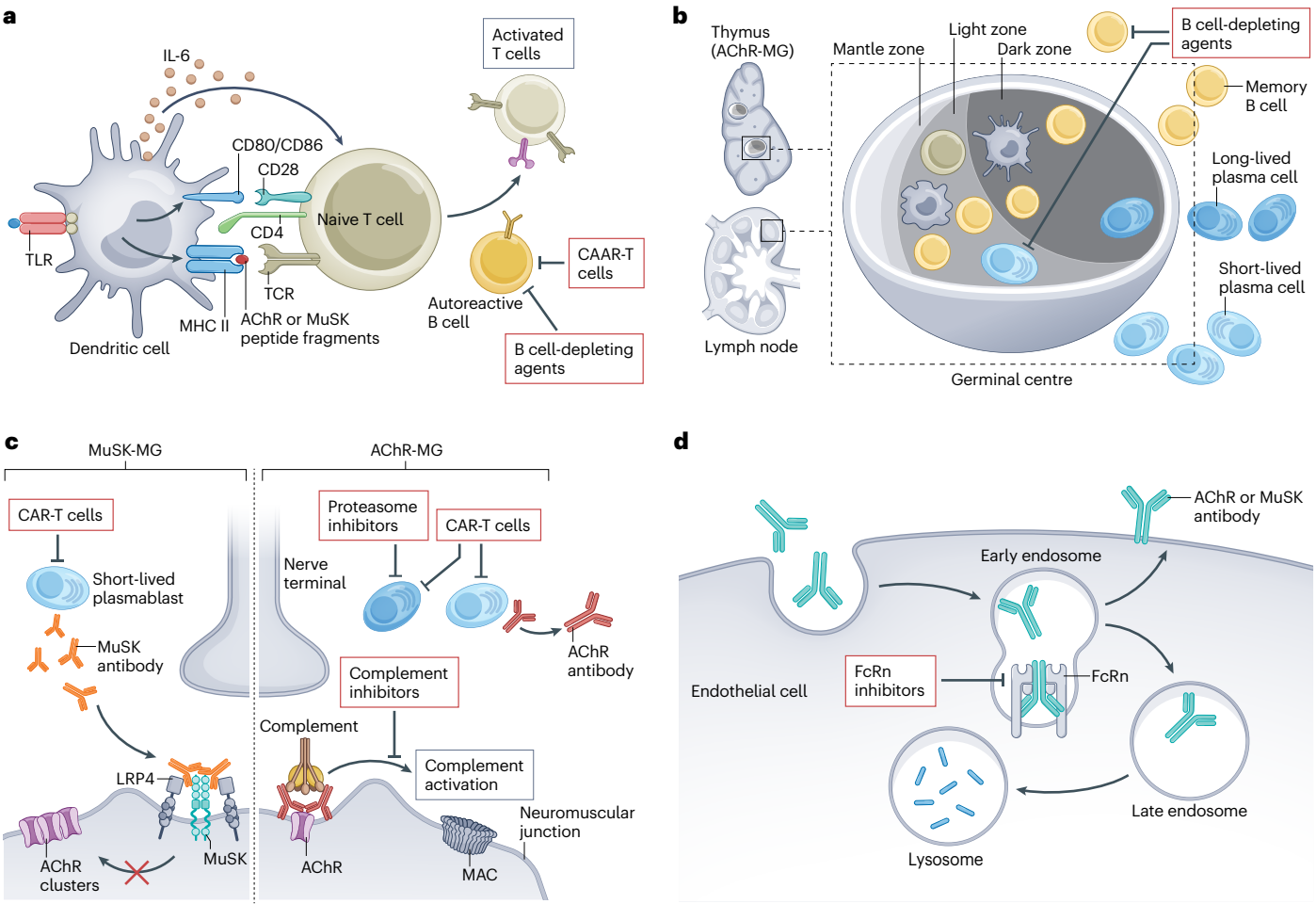

Fig. 1 | Immunopathogenesis of AChR-MG and MuSK-MG, and therapeutic targets. Various immune cells and pathways are involved in myasthenia gravis (MG) associated with acetylcholine receptor (AChR) antibodies (AChR-MG) and muscle-specific kinase (MuSK) antibodies (MuSK-MG). **a**, Dendritic cells and other antigen-presenting cells, located within the thymus and lymph nodes, initiate the immune response by presenting peptide fragments of muscle AChR or MuSK, alongside costimulatory molecules such as CD80 and CD86, to T cells. Inappropriate activation of Toll-like receptor (TLR) pathways might initiate or promote the autoimmune responses. Activated $CD4^+$ T cells initiate B cell activation and differentiation in the germinal centres of both the thymus and lymph nodes, generating AChR-specific or MuSK-specific B cells. **b**, In the germinal centres, pathogenic B cells and plasma cells are produced, contributing to the autoimmune response. The effector cells, including memory B cells, plasmablasts and plasma cells, actively secrete AChR or MuSK antibodies into the circulation. **c**, In AChR-MG, AChR antibodies bind to the AChR expressed at the neuromuscular junction, leading to complement activation and impairment of neuromuscular transmission. In MuSK-MG, MuSK antibodies target and bind to MuSK proteins at the neuromuscular junction, altering the LRP4–MuSK signalling pathway that is critical for the formation of AChR clusters and ultimately leading to impairment of neuromuscular transmission. **a**–**d**, Therapeutic agents target different stages of the disease process. Chimeric autoantibody receptor T (CAAR T)-cells (part **a**) have been designed to recognize and deplete MuSK-specific B cells. B cell-depleting agents (part **b**) specifically target B cells, leading to their depletion and subsequent reduction in autoantibody production. Proteasome inhibitors (part **c**) specifically target plasma cells, thereby reducing the production of pathogenic antibodies. Chimeric antigen receptor T (CAR-T) cells (part **c**) express synthetic receptors that target and deplete plasma cells and other B cells. Complement inhibitors (part **c**) mitigate complement-mediated neuromuscular damage initiated by AChR antibodies. Neonatal Fc receptor (FcRn) inhibitors (part **d**) reduce levels of circulating pathogenic antibodies by disrupting IgG recycling and promoting their degradation in the lysosome. LRP4, lipoprotein receptor protein 4; MAC, membrane attack complex; MHC, major histocompatibility complex; TCR, T cell receptor.

role of the thymus in AChR-MG pathophysiology (Fig. 1). A single-cell phenotyping study of thymus tissue from people with MG revealed aberrations in memory T_H cell subsets, particularly T_HCD103^+ and T_H cells expressing granulocyte–macrophage colony-stimulating factor (T_HGM)[14]. The thymic retention and diminished peripheral presence of T_HCD103^+ and T_HGM subsets are inversely related to disease severity[14].

The presence of intrathymic lymphoid follicles and germinal centres[50] in people with early-onset MG strongly supports the pathogenic role of the thymus in this subtype of MG. Furthermore, thymectomy often leads to substantial clinical improvements and reduced dependency on steroids in individuals with hyperplasia[51]. In individuals with thymic hyperplasia, aberrant B cell selection and somatic

hypermutation within the thymic germinal centres result in the generation of self-reactive B cells, which produce AChR-specific antibodies[52]. However, the exact triggers of intrathymic germinal centre development are currently unknown. A role for toll-like receptors in the initiation of intrathymic autoimmune response has been proposed[53,54]. The autosensitization process involves the participation of TECs, professional antigen-presenting cells and myoid cells expressing AChR, collectively contributing to the formation of germinal centres[25].

Autoantibody-producing B cells can be found in various tissue compartments beyond the thymus in both early-onset and late-onset MG; in vitro studies of cells from people with MG have demonstrated the presence of AChR autoantibody-producing B cells in the peripheral blood, lymph nodes and bone marrow[33,55–58]. Deep phenotyping of AChR autoantibody-producing thymic and circulating B cells would provide valuable insights into the immunopathogenesis of AChR-MG.

MG associated with MuSK antibodies

MG associated with antibodies specific to MuSK is a rare disease characterized by distinct pathogenic mechanisms and clinical characteristics. MuSK is a single-pass transmembrane protein that has a crucial role in the formation and maintenance of the neuromuscular junction and the clustering of AChR[59]. On activation, MuSK triggers a cascade of intracellular events that serve multiple functions related to synaptic transmission. First, MuSK orchestrates the aggregation and stabilization of AChRs along with other muscle proteins that are essential for synaptic transmission. Second, MuSK augments the transcriptional activity of genes responsible for encoding synaptic proteins within specialized muscle nuclei, termed synaptic nuclei. Last, MuSK facilitates the generation of retrograde signalling mechanisms that promote presynaptic differentiation. In the absence of MuSK activity, the formation of neuromuscular synapses is compromised[60–62]. The agrin-mediated activation of the LRP4–MuSK complex is a key process in neuromuscular junction development, where agrin binds to LRP4, activating MuSK, which in turn triggers AChR clustering on the muscle cell membrane through activation of the intracellular proteins Dok7 and rapsyn[63].

In MuSK-MG, the pattern of muscle weakness differs from that observed in AChR-MG, primarily affecting the neck and respiratory muscles and often leading to respiratory crises[64]. In addition, people with MuSK-MG frequently exhibit an atrophied tongue[65]. MuSK-MG has a higher prevalence in populations living closer to the equator and most commonly occurs in individuals in the age range 30–39 years[66]. Unlike AChR-MG, MuSK-MG is rarely reported in individuals over the age of 70 years[67]. In early stages of MuSK-MG, involvement of bulbar muscles is more common than in AChR-MG[67].

MuSK antibodies predominantly belong to the IgG4 subclass and do not activate complement[20]. MuSK antibodies have been shown to bind to the extracellular domain of MuSK, preventing interaction with LRP4, which in turn blocks the activation of Dok7 and rapsyn with consequent dispersal of AChR clusters[68]. A decrease in MuSK antibody titres following anti-CD20 treatment highlights the important role of short-lived plasma cells in MuSK-MG immunopathogenesis[20]; these cells, characterized by the expression of the CD20 molecule on their surface, are instrumental in the production of MuSK IgG4 antibodies (Fig. 1).

IgG4 antibodies participate in a stochastic phenomenon known as 'Fab-arm exchange', a process characterized by the random and reciprocal swapping of Fab arms among IgG4 molecules in the serum[69], leading to the generation of functionally bispecific, yet monovalent antibodies. The monovalent nature of the resultant IgG4 prevents antigen crosslinking and internalization, giving the antibodies a distinctive non-inflammatory profile. In a 2019 study, monovalent MuSK-specific monoclonal antibodies decreased MuSK phosphorylation and AChR clustering in response to agrin[70]. By contrast, bivalent, monospecific MuSK antibodies demonstrated an unanticipated agonistic effect, enhancing MuSK phosphorylation and facilitating AChR clustering independent of agrin[70]. These observations underscore the multifaceted pathogenicity of anti-MuSK IgG4, which is contingent on the antibody's valency and subclass.

Seronegative MG

Approximately 10% of people diagnosed with MG lack detectable antibodies specific to AChR, MuSK or LRP4 — categorized as 'seronegative' MG (SNMG). However, the widespread adoption of cell-based assays in the past 5 years has improved the diagnostic sensitivity of AChR and MuSK antibody testing, contributing to a decrease in SNMG diagnoses[71]. The absence of a recognized target antigen hinders our understanding of the pathological mechanisms involved in SNMG. Nonetheless, a 2020 study identified consistent complement deposits at motor endplates in individuals with SNMG[72]. This histopathological evidence highlights the involvement of the complement system in SNMG and bears important implications for both diagnosis and therapy. For people with refractory SNMG, a biopsy of the external intercostal muscles alongside histopathological analysis might aid the differential diagnosis and refine therapeutic strategies.

Standard therapy

The treatment for MG is individualized and depends on several factors, including age, gender, comorbid conditions, the rate of symptom progression, the presence of respiratory and bulbar involvement, and the presence of AChR or MuSK antibodies[7,73–75]. The primary objective of treatment is to improve functional ability and quality of life by minimizing the severity of MG symptoms to the point of minimal manifestations, while also avoiding considerable drug-induced adverse effects. The existing standard of care in the management of MG typically involves the use of AChE-I as first-line treatment (Fig. 2). Thymectomy is a standard procedure routinely performed in individuals diagnosed with generalized AChR-MG who are under 50 years of age or have thymoma-associated MG[2]. If the symptoms are not adequately controlled with AChE-I alone, oral corticosteroids are often added to the treatment regimen[2]. When tapering of corticosteroids proves unsuccessful or is not desirable, non-steroidal immunosuppressive therapies are frequently used as steroid-sparing agents[7]. These immunosuppressive agents, such as azathioprine, cyclosporine, mycophenolate mofetil or tacrolimus, can help to modulate the immune response and decrease the reliance on high doses of steroids[2,7].

Conventional treatment options for AChR-MG, such as intravenous immunoglobulin and AChE-I, have limited effectiveness in people with MuSK-MG[7]. These individuals often exhibit clinical and electrophysiological evidence of cholinergic hypersensitivity upon administration of AChE-I[76]. AChE-I do not substantially improve muscle strength in most people with MuSK-MG; indeed, these drugs can sometimes precipitate a paradoxical exacerbation of weakness, potentially leading to a cholinergic crisis in some individuals[66,67]. Symptom management of MuSK-MG often requires prolonged and high-dose steroid administration, which can pose challenges during the tapering process[67]. Notably, 3,4-diaminopyridine can offer potential benefits in certain individuals with MuSK-MG[77].

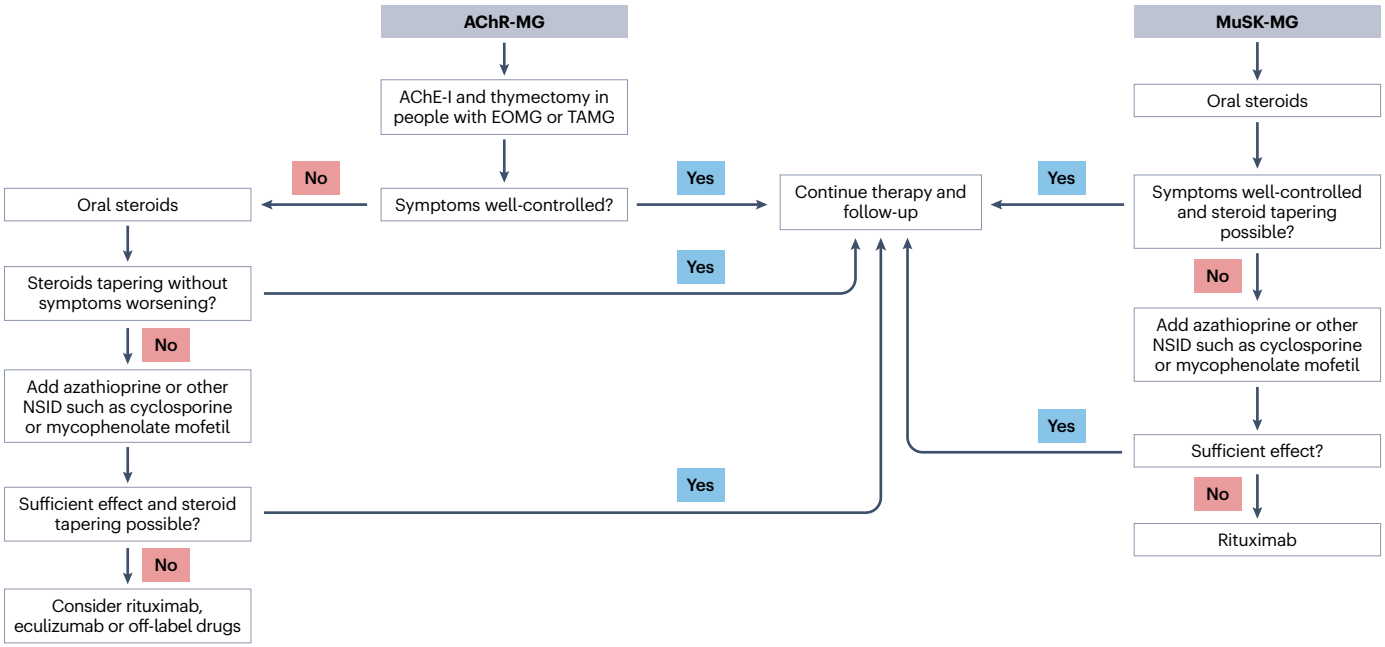

Fig. 2 | Standard therapy algorithm for the management of AChR-MG and MuSK-MG. The algorithm details traditional decision-making for the management of myasthenia gravis (MG) associated with acetylcholine receptor (AChR) antibodies (AChR-MG) or muscle-specific kinase (MuSK) antibodies (MuSK-MG) with standard therapies. AChE-I, AChE inhibitor; EOMG, early-onset MG; NSID, non-steroidal immunosuppressive drugs; TAMG, thymoma-associated MG.

Plasma exchange and intravenous immunoglobulin are traditionally used as rescue therapies in people experiencing myasthenic crisis; however, in those who are refractory to standard treatment, these interventions can occasionally be employed as long-term therapies[78]. Although immunosuppressive therapies are considered as established treatments for MG, they come with several drawbacks, including a heightened vulnerability to severe infections with potentially life-threatening consequences, adverse systemic effects, a delayed onset of action, and a small yet significant long-term risk of developing malignancies and drug-related toxicity[79,80]. Despite their historical usage and continued prevalence in MG management, these treatments present considerable limitations in terms of safety and long-term risks.

Biologics and new molecular therapies

The treatment landscape for MG has evolved with the introduction of biologics and new molecular therapies. These treatments are designed to selectively target components of the immune system implicated in MG pathophysiology. This approach aims to achieve efficacy in symptom management alongside potentially reducing the side effects commonly associated with broader immunosuppressive therapies. A detailed comparison of these novel therapeutic agents, including their specific mechanisms of action and evidence-based efficacy and safety profiles, is provided in Table 2.

B cell-depleting agents

Rituximab. Rituximab is a widely used anti-B cell agent, initially approved as a therapy for non-Hodgkin B cell lymphomas[81]. The therapeutic potential of rituximab in autoimmune disorders has been extensively investigated owing to the important role of B cells in autoimmunity[82]. The drug has demonstrated efficacy in rheumatoid arthritis[83] and has subsequently been investigated in other autoimmune disorders affecting the central and peripheral nervous systems[84]. Rituximab is a chimeric monoclonal antibody consisting of human and murine components specific to CD20, a phosphoprotein expressed on the surface of all B cells, excluding stem cells, progenitor B cells and plasma cells[85]. The exact physiological function of CD20 is still largely unknown, although a 2021 study revealed its role as a gatekeeper for maintaining the resting state of naive B cells[86]. Rituximab depletes circulating B cells, but its impact on B cells in the bone marrow, lymph nodes and thymus is still being investigated and requires further elucidation[87,88].

Across several open-label studies, rituximab has demonstrated efficacy in alleviating disability in 50–80% of participants with MG when administered at a dose of 375 mg/m^2 once weekly for 4 weeks or 1 g biweekly[89,90]. The efficacy of rituximab is particularly remarkable in individuals with MuSK-MG[89]. In a multicentre, blinded, prospective study, 58% (14/24) of participants treated with rituximab achieved a status of minimal manifestations requiring only low-dose immunosuppressive therapy, compared with 16% (5/31) of participants not treated with rituximab[91]. Furthermore, a retrospective nationwide study conducted in Austria reported remission rates of 26% at 3 months and 43% at a median of 20 months in individuals with AChR-MG or MuSK-MG treated with various dosing protocols of rituximab[92].

The response of people with AChR-MG to rituximab seems to be heterogeneous; a study published in 2020 suggests that rituximab is more effective, even at a low dose, in individuals who are newly diagnosed with AChR-MG, compared with those with AChR-MG at later stages[93]. In the BeatMG study[94], a prospective, randomized, double-blind, placebo-controlled clinical trial of B cell-targeted treatment in people with MG, rituximab was shown to be well-tolerated and safe, but did not show a significant steroid-sparing effect compared

with placebo. A futility analysis of the results from a larger phase III trial in people with mild to moderately symptomatic generalized AChR-MG showed that rituximab treatment is unlikely to demonstrate a clinically meaningful improvement, defined as 30% steroid-sparing effect over placebo[94]. By contrast, in the randomized, controlled RINOMAX study[95], a single 500 mg dose of rituximab was associated with a higher likelihood of minimal manifestations and a decreased requirement for rescue medications compared with placebo. The study's primary outcome to achieve minimal disease manifestations by week 16 was attained in 71% (17/24) of participants in the rituximab group, whereas only 29% (6/21) participants in the placebo group achieved the same outcome. Consistent with this result, the rituximab group outperformed the placebo group in meeting the same criteria at weeks 24, 36 and 48 (ref. 95).

In summary, rituximab is a very effective therapy in individuals with MuSK-MG and could have a role as a therapeutic option in the early stages of the disease in people with AChR-MG. Exploring the determinants of a poor response to rituximab in people with AChR-MG could provide valuable insights into the immunobiology of this subtype of MG. A 2020 study suggested that the persistent presence of antibody-secreting cells that are not depleted by rituximab is responsible for disease recurrence following rituximab therapy[96].

Other biologics targeting B cells

The development of several monoclonal antibodies that target B cells has greatly expanded the therapeutic options for immune-mediated diseases and haematological neoplasms. Ocrelizumab[97], a recombinant humanized monoclonal antibody specific to CD20, and ofatumumab[98],

Table 2 | Molecular therapies for myasthenia gravis

Drug name	Clinical trial	Mechanism	Dosing schedule	Treated participants (*n*)	Key efficacy measures (treatment vs placebo)	FDA approval for MG
Complement inhibitors						
Eculizumab	REGAIN[111]	Inhibits C5 activation and terminal complement/MAC formation	Loading 900 mg IV weekly for 4 weeks; maintenance 1,200 mg IV every 2 weeks	Total, 125 (placebo, 63; eculizumab, 62)	MG-ADL −4.2 vs −2.3 (P=0.0058); QMG −4.6 vs −1.6 (P<0.0006)	Yes
Ravulizumab	CHAMPION MG[121]	Inhibits C5 activation and terminal complement/MAC formation	Variable dosing based on weight	Total, 175 (placebo, 89; ravulizumab, 86)	MG-ADL −3.1 vs −1.4 (P<0.001); QMG −2.8 vs −0.8 (P=0.001)	Yes
Zilucoplan	RAISE[125]	Short 35 kDa macrocyclic peptide targeting C5/C5b; inhibits terminal complement/MAC formation	0.3 mg/kg BW daily SC injections	Total, 174 (placebo, 86; zilucoplan, 88)	MG-ADL −4.43 vs −2.31 (P<0.001); QMG: −6.32 vs −3.25 (P<0.001)	Yes
FcRn Antagonists						
Efgartigimod	ADAPT[132]	Reduces autoantibody levels	10 mg/kg BW IV once weekly for 4 weeks	Total, 167 (placebo, 84; efgartigimod 83); AChR-MG, 129 (placebo, 64; efgartigimod, 65); MuSK-MG, 6 (placebo, 3; efgartigimod, 3); seronegative MG, 32 (placebo, 16; efgartigimod, 16)	Results for total cohort: MG-ADL −4.45 vs −1.84 (P<0.001); QMG −6.21 vs −1.01 (P<0.001)	Yes
Rozanolixizumab	MycarinG[134]	Reduces autoantibody levels	7 or 10 mg/kg BW SC weekly for 7 weeks	Total, 200 (placebo, 67; rozanolixizumab 7 mg/kg, 66; rozanolixizumab 10 mg/kg, 67); AChR-MG, 179 (placebo, 59; rozanolixizumab 7 mg/kg, 60; rozanolixizumab 10 mg/kg, 60); MuSK-MG, 21 (placebo, 8; rozanolixizumab 7 mg/kg, 5; rozanolixizumab 10 mg/kg, 8)	Results for total cohort: MG-ADL −3.50 vs −0.91 (P<0.001); QMG −4.32 vs −0.84 (P<0.001)	Yes
Anti-CD20						
Rituximab	BEAT-MG[94]	Depletes CD20 expressing B lymphocytes	One cycle every 6 months; 375 mg/m^2 IV weekly for 4 weeks	Total, 52 (placebo, 27; rituximab, 25)	Steroid-sparing effect[a]: 60% vs 56%	No
Rituximab	RINOMAX[95]	Depletes CD20 expressing B lymphocytes	500 mg IV single infusion at baseline	Total, 47 (placebo, 22; rituximab, 25)	MM at 16 weeks: 71% (17 of 24) in the rituximab group vs 29% (6 of 21) in the placebo group (P=0.007; probability ratio 2.48, 95% CI 1.20–5.11)	No

BW, body weight; IV, intravenous infusion; MAC, membrane attack complex; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living score; MM, minimal manifestations of disease; QMG, Quantitative Myasthenia Gravis score; SC, subcutaneous injection. [a]Steroid-sparing effect defined as ≥75% reduction in mean daily prednisone dose in the 4 weeks prior to week 52.

a fully human anti-CD20 monoclonal antibody, have received approval in several countries for the treatment of multiple sclerosis, an immune-mediated disease of the CNS. As a humanized molecule, ocrelizumab is anticipated to have lower immunogenicity than rituximab. Ofatumumab dissociates from its target at a slower rate than rituximab and binds a different membrane-proximal epitope[99]. The treatment is available as a subcutaneous injection that can be self-administered at home, making this an appealing therapeutic option. Ublituximab, another effective anti-CD20 monoclonal antibody, was approved by the FDA in 2022 for the treatment of multiple sclerosis[100]. Ublituximab is administered twice-yearly after the initial doses, and thus will potentially improve adherence to treatment owing to the less frequent dosing schedule than with other therapies. The glycoengineered crystallizable fragment (Fc) region of ublituximab exhibits a strong affinity for the Fcγ receptor IIIa, which is associated with heightened antibody-dependent cellular cytotoxicity activity, an immune response where natural killer cells induce the lysis of antibody-coated target cells[101].

An urgent need exists to conduct well-designed and rigorous clinical trials involving novel anti-CD20 therapeutics, especially in people with MuSK-MG, who are most likely to experience substantial benefits from these therapeutic interventions. Such a trial is being conducted to investigate inebilizumab, a humanized IgG1κ monoclonal antibody with high affinity for CD19. Although plasma cells express low levels of CD19 protein, the antibody effectively triggers antibody-dependent cellular cytotoxicity, resulting in the elimination of nearly all other B cells, including precursor plasma cells[102]. Following approval in several countries for the treatment of neuromyelitis optica spectrum disorders, which share common immunopathogenic mechanisms with MG[103], a phase III randomized, placebo-controlled trial is currently underway to assess the safety and efficacy of inebilizumab in people with AChR-MG or MuSK-MG.

Complement inhibitors

Complement inhibitors are emerging as effective therapies for the treatment of people with AChR-MG[104]. Complement activation has a fundamental role in the morphological changes that occur at the neuromuscular junction in MG. Therefore, interventions that target the regeneration and stabilization of the postsynaptic membrane at the neuromuscular junction hold promise for improving and modifying the course of MG. Biomarkers of neuromuscular junction degeneration could be useful to monitor the therapeutic effect of complement inhibition.

Importantly, complement receptors are expressed on several immune cell subsets, including B and T lymphocytes, as well as dendritic cells[105]. One study provided insights into the involvement of complement in adaptive immunity[106], supporting the hypothesis that inhibiting complement activation can also have an impact on T and B cell subsets in people with MG[107]. Further investigations are needed to explore the effect of complement inhibition on immune cells in MG.

Eculizumab. Eculizumab is a humanized monoclonal antibody that targets the C5 complement protein by blocking the process of C5 cleavage into C5a and C5b, effectively inhibiting the formation of the C5b-9 MAC[108]. Eculizumab was the first available drug that specifically targets the complement system, particularly C5. Eculizumab was initially approved by the FDA in 2007 for the treatment of paroxysmal nocturnal haemoglobinuria (PNH), a rare acquired disorder characterized by complement-mediated intravascular haemolysis and haemoglobinuria[109], and then as a therapy for atypical haemolytic uraemic syndrome (aHUS)[110]. In 2017, eculizumab was approved for the treatment of generalized MG[111], and for the treatment of neuromyelitis optica in 2019 (ref. 112).

In a large phase III trial called REGAIN[111], 125 participants with refractory generalized MG were randomly assigned to receive either intravenous eculizumab or placebo as an add-on medication to their existing immunosuppressive treatments, excluding plasmapheresis and intravenous immunoglobulin. The dosing plan included an induction phase with 900 mg administered on days 0, 7, 14 and 21, followed by a dose of 1,200 mg at week 4 and maintenance dosing of 1,200 mg every 2 weeks for 26 weeks[111]. No significant difference was observed in the primary efficacy end point, which was the change in total Myasthenia Gravis Activities of Daily Living (MG-ADL) score compared with placebo, measured using worst-rank analysis of covariance. However, other noteworthy improvements were observed with eculizumab treatment compared with placebo across various secondary end point measures, including changes in the MG-ADL score, the Quantitative Myasthenia Gravis (QMG) score and the 15-item Myasthenia Gravis Quality of Life score, which were calculated using analysis of variance for repeated measures[111]. Furthermore, in the open-label extension of the REGAIN study, 88% of participants treated with eculizumab achieved an improved status and 57% achieved minimal manifestation status after 130 weeks of treatment[113]. In addition, treatment with eculizumab significantly improved perceived fatigue, compared with a placebo, in people with MG[114].

The use of eculizumab carries a significant risk of meningococcal meningitis[115], emphasizing the importance of immunization before starting eculizumab therapy. Vaccination against *Neisseria meningitidis* is recommended at least 2 weeks prior to initiating treatment, and revaccination should be considered after 2–5 years[116]. If vaccination is not feasible prior to starting treatment, prophylactic antibiotics should be prescribed until 2 weeks after vaccination. Despite this precaution, people on long-term immunosuppressive therapy might not produce an adequate immune response to vaccination, and testing for neutralizing antibodies against *N. meningitidis* serogroups is not routinely performed in clinical practice. The need for vaccine boosters should be carefully assessed in each patient undergoing treatment with complement inhibitors[117].

Eculizumab has shown significant benefits in people with treatment-resistant generalized MG. Nevertheless, up to 15% of individuals do not respond to treatment[111]. This lack of response might be attributed to C5 polymorphisms[118] and the presence of other pathogenic mechanisms, including antibody-mediated AChR blocking and/or internalization, which could account for the observed variability in patient outcomes.

Ravulizumab. Ravulizumab is a long-acting complement C5 inhibitor that targets the same epitope as eculizumab but has a longer elimination half-life[119], allowing maintenance dosing at intervals of 8 weeks. Approved originally for the treatment of PNH[120] and aHUS[110], in 2022 ravulizumab obtained approval in several countries for use in adults with generalized AChR-MG. The CHAMPION MG study, a randomized, controlled phase III trial, evaluated the efficacy and safety of ravulizumab in people with AChR-MG. The study included 175 participants, with 86 receiving ravulizumab and 89 receiving placebo[121]. The cohort demographics, including gender distribution and average age, were balanced between the two groups. At the end of the 26-week treatment period, ravulizumab demonstrated a substantial increase in the magnitude of mean changes in MG-ADL score from baseline to week 26

compared with the MG-ADL score in the placebo group. Ravulizumab treatment led to significantly greater reductions in MG-ADL and QMG total scores compared with the reductions in the placebo group[121]. The improvements in MG-ADL and QMG scores were evident from the first week of treatment and were sustained throughout the 26-week study period for both the placebo and ravulizumab groups. While improvements in quality of life were greater in individuals treated with ravulizumab than in those receiving placebo, the differences were not statistically significant after 26 weeks of treatment[121].

In the CHAMPION MG trial, the incidence of adverse effects, which were mostly mild, was comparable between the two groups and not considered treatment-related[121]. Overall, the study demonstrated the effectiveness and acceptable safety profile of ravulizumab in people with AChR-MG, providing promising results for the treatment of this condition. Like eculizumab, ravulizumab treatment is associated with an elevated risk of *N. meningitidis* infection[122]. As a precautionary measure, prioritizing vaccination and considering prophylactic antibiotic treatment is imperative in all patients undergoing ravulizumab therapy.

Zilucoplan. Zilucoplan, a synthetic macrolide, exhibits a strong affinity for C5, inhibiting cleavage of the complement protein[123] and offering a potential treatment option for complement-mediated disorders. The drug also effectively blocks the interaction of preformed C5b with C6 complement[123], adding to its unique mechanism of action. Zilucoplan was initially developed as an alternative for individuals with PNG who are eculizumab-resistant[124]. Advantages of the drug include self-administration, rapid action and subcutaneous dosing[124], each of which enhances the convenience of the treatment.

The efficacy and safety of zilucoplan for the treatment of MG was evaluated in the RAISE study, a randomized, double-blind, placebo-controlled phase III trial[125]. A total of 174 participants were randomly assigned to receive zilucoplan ($n = 86$) at a dose of 0.3 mg/kg or placebo ($n = 88$). Individuals treated with zilucoplan exhibited a significantly greater reduction in MG-ADL score from baseline to week 12 (least squares mean change −4.39) compared with those who received the placebo (least squares mean change −2.30)[125]. A significant improvement in MG-ADL score was observed within the first week of zilucoplan treatment, which increased until week 4 and was sustained to week 12 (ref. 125). Overall, the trial results demonstrated prompt and clinically significant improvements in MG-specific efficacy outcomes with zilucoplan treatment. The treatment also exhibited a favourable safety profile and high tolerability, apart from injection site bruising that occurred in 14 subjects (16%) in the zilucoplan group and in eight individuals (9%) in the placebo group[125].

A unique characteristic of zilucoplan, being a peptide, is its inability to undergo the IgG recycling pathway (as explained in the section 'Neonatal Fc receptor inhibitors'), rendering it unaffected by neonatal Fc receptor (FcRn) inhibitors. This characteristic presents an opportunity to combine the treatment with therapies that specifically target the FcRn, opening new possibilities for synergistic treatment approaches. In line with other complement inhibitors, all people undergoing treatment with zilucoplan should receive vaccination against *N. meningitidis*.

Neonatal Fc receptor inhibitors

The FcRn belongs to the family of MHC I-related receptors and is encoded by the *FCGRT* gene[126]. FcRn receptors are expressed in different cell types including endothelial cells, antigen-presenting cells and epithelial cells[126]. A primary role of the receptors is to extend the half-life of serum IgG by protecting the IgG from degradation in lysosomes[126]. This function involves the pH-dependent binding of FcRn to IgG, which occurs under acidic conditions in the lysosome following the internalization of IgGs into the cell by pinocytosis[126]. The binding of FcRn shields IgG from degradation by lysosomal enzymes and subsequently transports IgG back to the cell surface where the neutral pH leads to its release, facilitating extended circulation of the IgG in the bloodstream[126]. This pH-dependent binding mechanism plays an essential part in prolonging the half-life of IgG antibodies, which typically circulate approximately four times longer than IgM or IgA antibodies[127]. Equally, this process has a crucial role in prolonging the lifespan of pathogenic IgG, contributing to the development of IgG-mediated autoimmune disorders such as MG. Therefore, inhibiting FcRn to promote the degradation of pathogenic IgG represents a potential therapeutic strategy for MG.

Extended use of FcRn inhibitors might cause sustained hypogammaglobulinaemia, resulting in the reduction of both protective and pathogenic antibodies, which could lead to an increased risk of infections[128]. The binding of IgG immunocomplexes to FcRn expressed on the surface of myeloid cells stimulates the production of pro-inflammatory cytokines[128]. Moreover, FcRn has been demonstrated to have an important role in the internalization and trafficking of IgG immunocomplexes[126]. Specifically, in antigen-presenting cells, FcRn directs IgG immunocomplexes to the endolysosomal compartment where the antigen undergoes degradation into peptide fragments that are subsequently loaded onto MHC II to activate $CD4^+$ T cells[129]. In addition, a specific subset of dendritic cells that express CD141 have been shown to use FcRn for the recycling and cross-presentation of antigens derived from circulating immunocomplexes in association with MHC I to activate $CD8^+$ T cells[130]. Further studies are required to determine the involvement of FcRn-mediated antigen processing in MG and other autoimmune diseases. A conceivable hypothesis is that inhibiting FcRn-mediated antigen processing in the early stages of MG could limit epitope spreading and hinder the chronic progression of the autoimmune response.

Efgartigimod. Between 2021 and 2023, efgartigimod, a humanized IgG1 Fc fragment that binds with high affinity to the FcRn[131], received regulatory approval in multiple countries for the treatment of AChR-MG. The decision followed the success of a phase III randomized, controlled, multicentre study, ADAPT, in which efgartigimod met its primary end point[132]. The study included a total of 167 participants, with 84 receiving efgartigimod intravenously once a week for 4 weeks and 83 receiving a placebo. After the initial treatment cycle, participants could undergo additional cycles depending on their individual clinical response as determined by two factors: first, achieving a minimum MG-ADL score of ≥5, and second, in those who were MG-ADL responders (defined as those who showed an improvement of two points or more in their total MG-ADL score) but no longer showed the same level of improvement in their total MG-ADL total score[132]. Subsequent cycles were not initiated until at least 8 weeks had passed since the initiation of the previous cycle. Among the entire study cohort, 77% of participants ($n = 129$) were diagnosed with AChR-MG and 23% ($n = 38$) were AChR antibody-negative, of whom six were MuSK antibody-positive[132].

In people with AChR-MG treated with efgartigimod, MG-ADL scores improved by at least two points for four consecutive weeks in 68% of individuals (44/65 participants), compared with 30% (19/64 participants) in the placebo group. Notably, among people with AChR-MG treated with efgartigimod, 40% experienced minimal or no symptoms,

as defined by a MG-ADL score of 0 or 1, compared with only 11% in the placebo group[132]. In summary, efgartigimod demonstrates strong efficacy in improving MG symptoms and has an acceptable safety profile. Furthermore, the treatment can be tailored to each individual, offering the potential for personalized treatment strategies. However, the identification of biomarkers is urgently required to determine the optimal timing of therapy cycles before clinical deterioration becomes apparent; this development would improve the long-term management of MG.

Rozanolixizumab. Rozanolixizumab is a humanized IgG4 monoclonal antibody that specifically targets the IgG-binding region of FcRn[133]. The antibody received approval from the FDA in 2023 for the treatment of generalized AChR-MG and MuSK-MG. The Mycarin G clinical trial, a double-blind, randomized controlled phase III study, aimed to assess the efficacy and safety of rozanolixizumab in treating MG[134]. The trial included 200 participants with generalized MG who were randomly assigned to receive either 7 mg/kg or 10 mg/kg of rozanolixizumab or placebo, each administered subcutaneously once a week. The MG-ADL score from baseline to day 43 — the primary end point — was similarly reduced by both doses of rozanolixizumab: least-squares mean changes of −3.37 in the 7 mg/kg group and −3.40 in the 10 mg/kg group, as compared with −0.78 in those treated with placebo[134]. In addition, significant improvements were observed in secondary end points, including QMG and MG composite scores, among participants who received both doses of rozanolixizumab, further supporting the potential benefits of this treatment in managing MG.

Interestingly, improvements were observed in all 21 participants with MuSK-positive MG included in the Mycarin G trial[134]. Improvements were characterized by rapid reductions in total IgG levels as early as day 8, although these levels had returned to baseline by day 99. The therapeutic impact of rozanolixizumab in MuSK-MG is intriguing and deserves further investigation. Notably, rozanolixizumab has been demonstrated to induce dose-dependent reductions in all four IgG subclasses, including IgG4 (ref. 135). This finding might help explain the therapeutic potential of rozanolixizumab in treating MuSK-MG.

In the Mycarin G trial, treatment-related adverse events were reported by 81% (52/64 participants) and 83% (57/69 participants) of participants treated with 7 mg/kg and 10 mg/kg rozanolixizumab, respectively, compared with 67% (45/67 participants) of those treated with placebo[134]. Although the frequency of adverse events was high, the rate of serious adverse events was low and similar among the study arms[134]. The most common adverse events were headache, diarrhoea, pyrexia and nausea[134].

Other FcRn inhibitors. Other FcRn inhibitors have been developed and are currently being investigated. Encouraging safety and efficacy results have emerged from the Vivacity-MG trial, a phase II randomized, placebo-controlled study evaluating nipocalimab in adults with generalized MG[136]. A phase III study is currently underway to further evaluate the potential benefits of nipocalimab in people with MG.

Another FcRn inhibitor currently in phase III clinical trials for induction and maintenance therapy in people with generalized MG is batoclimab, a fully human IgG1 monoclonal antibody. The Fc portion of the antibody has been modified to reduce antibody-dependent cell-mediated cytotoxicity[137]. In phase II, batoclimab demonstrated a favourable safety and tolerability profile, with hypercholesterolaemia being the most common treatment-related adverse event[138].

Proteasome inhibitors

The immune system comprises long-lived memory plasma cells — a distinct population of terminally differentiated B cells characterized by the absence of cell surface markers such as CD20 (ref. 139). These plasma cells, which reside in specialized niches such as the bone marrow, play a vital part in maintaining adaptive immunity and act as sentinels of the immune response[139,140]. In addition, the cells exhibit resistance to a wide range of therapeutic agents, including rituximab[141], and therefore targeting these cells effectively is a considerable challenge.

Long-lived plasma cells are involved in intensive immunoglobulin synthesis and undergo substantial protein turnover[142], necessitating efficient degradation and elimination through the ubiquitin–proteasome pathway that is responsible for intracellular protein clearance[140,143]. Proteasome inhibitors induce the accumulation of misfolded proteins and trigger apoptosis in highly active plasma cells and are therefore effective in treating multiple myeloma[144,145].

Bortezomib, a proteasome inhibitor approved for treating multiple myeloma, was tested in a rat model of experimental autoimmune MG[146]. The treatment led to a reduction in AChR antibody titres compared with its effect in saline-treated rats and prevented ultrastructural damage to the postsynaptic membrane[146]. These findings highlight the potential of bortezomib as a therapeutic intervention in people with MG. Further studies are warranted to establish more comprehensive knowledge of the efficacy and safety of bortezomib. A notable limitation of bortezomib treatment is the potential development of peripheral neuropathy, which occurs in 30–40% of people undergoing bortezomib therapy and can be disabling and permanent in some individuals[147]. Managing adverse effects promptly is crucial for the optimal use of bortezomib in MG.

Interestingly, carfilzomib, a second-generation proteasome inhibitor, has improved efficacy and safety profiles[148]. Unlike bortezomib, which forms a reversible complex with the proteasome[149], carfilzomib binds irreversibly to the proteasome, specifically inhibiting its chymotrypsin-like activity[149]. To date, no studies of carfilzomib have been conducted in people with MG.

CAR-T and CAAR-T cell therapies

Adoptive cellular therapy (ACT) is an advanced form of immunotherapy that involves harvesting T cells from either the patient or a donor[150]. The T cells are then cultivated in a laboratory where they can be genetically modified to enhance the immune response against specific diseases or conditions upon reinfusion into the patient's body. Chimeric antigen receptor T (CAR-T) cell therapy is a type of ACT that is transforming the treatment paradigm for haematological neoplasms[151]. CAR-T cell therapy holds immense promise in revolutionizing the way we manage MG and other autoimmune diseases. This type of therapy has obtained FDA approval for the treatment of refractory B cell acute lymphocytic leukaemia, B cell lymphoma and non-Hodgkin lymphoma[152]. However, the potential extends beyond these indications and the therapy is expected to find broader applications in the fields of haemato-oncology and autoimmune diseases[153,154].

Descartes-08, an investigational RNA-based CAR-T cell therapy (rCAR-T), showed promising outcomes in a phase Ib/IIa clinical trial involving 14 adults with generalized MG[155]. This therapy specifically targets the B cell maturation antigen expressed in mature B lymphocytes and plasma cells. Infusions of Descartes-08 led to significant reductions in the severity of MG, as measured by the MG-ADL score, the QMG score, the MG composite score, and the revised 15-item Myasthenia Gravis Quality of Life score, over a follow-up period of up to 9 months.

The results of the trial demonstrated the therapy's ability to effectively alleviate disease symptoms while maintaining a favourable safety profile for up to 9 months following administration[155].

A noteworthy aspect of the Descartes-08 study is the successful preparation of autologous rCAR-T for individuals undergoing immunosuppressive therapy[155]. Moreover, rCAR-T cells were used without the need for lymphodepletion chemotherapy, typically administered prior to cell therapy to create a favourable immune and cytokine milieu for CAR-T expansion, further underscoring the feasibility of this approach. Descartes-08 exhibited a favourable safety profile without the occurrence of adverse effects commonly associated with DNA-based therapies such as neurotoxicity, cytokine release syndrome (CRS) and other blood-related abnormalities[155]. The remarkable safety profile observed in this trial has laid the foundation for an ongoing phase IIb study, which includes a placebo-controlled arm (NCT04146051).

Chimeric autoantibody receptor T (CAAR-T) cell therapy offers another similar therapeutic approach. Unlike CAR-T cells that express receptors specifically designed to target molecules expressed on pathological cells, CAAR-T cells express an extracellular autoantigen that is recognized by the B cell receptor of self-reactive B cells[156]. This innovative approach has shown efficacy in preclinical studies, particularly in pemphigus, an autoimmune disease of the skin[156]. In an experimental mouse model of MuSK-MG, T cells engineered to express a MuSK CAAR with CD137–CD3ζ signalling domains, referred to as MuSK-CAAR-T, have exhibited impressive abilities to deplete MuSK-specific B cells when compared with cells expressing a control vector. These findings highlight the potential of MuSK-CAAR-T as a targeted therapy for the management of MuSK-MG, bringing hope for improved treatment outcomes[157].

The primary side effect associated with CAR-T cell therapy is CRS, which can manifest as mild constitutional symptoms or progress to severe CRS, potentially resulting in multiorgan dysfunction[158]. Well-designed and highly specific CAAR-T cells should potentially lower the risk of CRS and off-target toxicity.

Concluding remarks and future challenges

Several new treatment options have emerged for people with MG, ushering in an exciting era of MG therapy accompanied by unique challenges (Fig. 3). One notable challenge is that many recently approved drugs discussed in this Review seem to target the later stages of

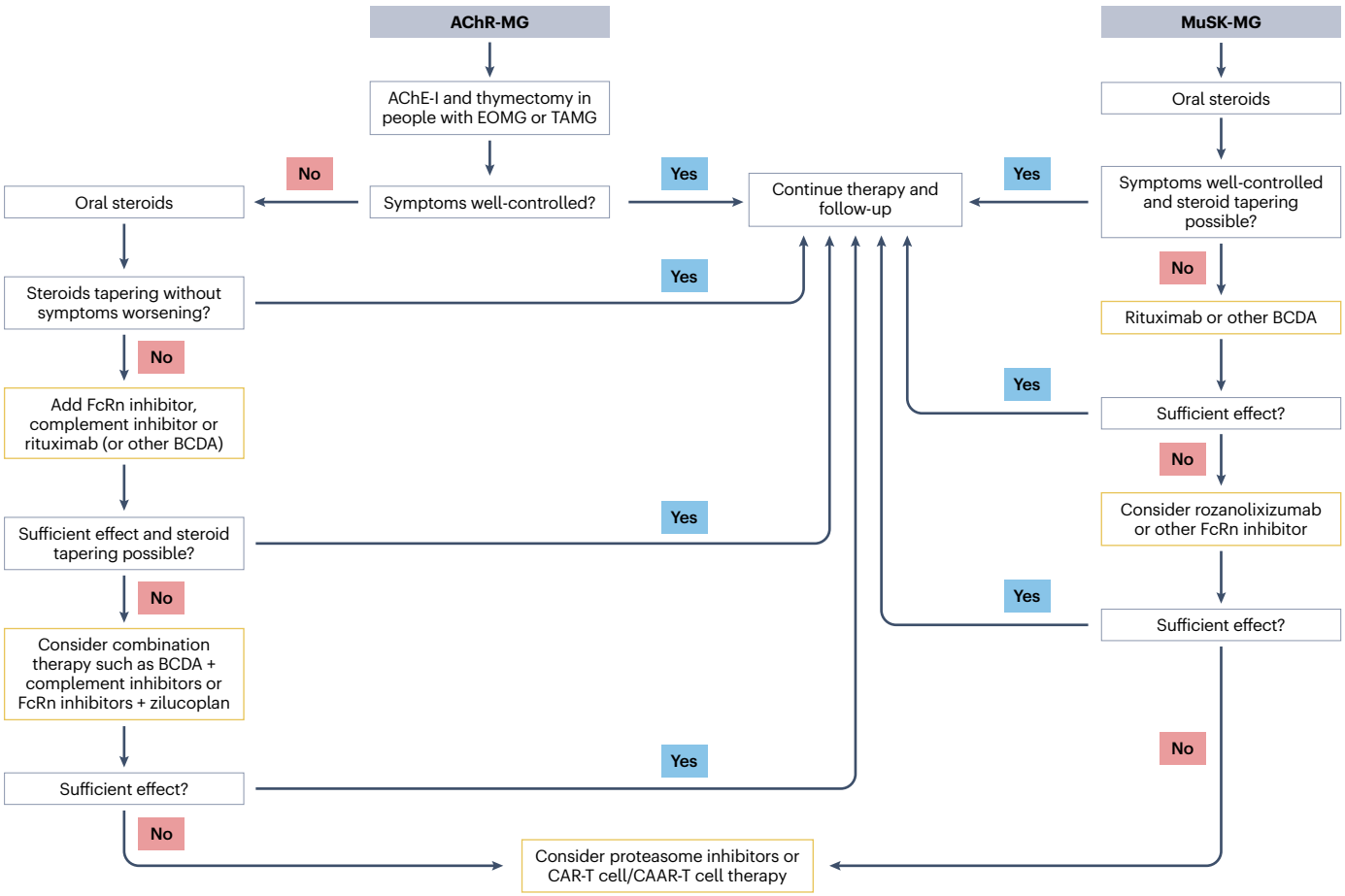

Fig. 3 | An algorithm for the management of AChR-MG and MuSK-MG incorporating new molecular therapies. New molecular therapies are now available for the management of myasthenia gravis (MG) associated with acetylcholine receptor (AChR) antibodies (AChR-MG) or muscle-specific kinase (MuSK) antibodies (MuSK-MG). The algorithm proposes a decision-making process incorporating the new molecular therapies (highlighted boxes) alongside standard therapies. AChE-I, acetylcholinesterase inhibitor; BCDA, B cell-depleting agent; CAAR, chimeric autoantibody receptor; CAR, chimeric antigen receptor; EOMG, early-onset MG; FcRn, neonatal Fc receptor; TAMG, thymoma-associated MG.

the pathological cascade, necessitating further evaluation of their disease-modifying potential. Moreover, in each of the phase III trials discussed here, some individuals exhibited limited or no response to the drug[94,95,111,121,125,132,134]. Such observations demand further investigation.

To date, no head-to-head clinical trials have been conducted to compare the efficacy of the new therapies discussed in this Review. Among the various molecular therapies that have shown efficacy in successful trials, acknowledging those that have failed is essential; belimumab — a monoclonal antibody against B lymphocyte stimulator — and iscalimab, which targets the CD40 antigen, have not shown efficacy in the treatment of MG. These findings highlight the ongoing challenges and gaps in our understanding of the immunobiology of MG. In the past decade, advances in cell phenotyping technologies, such as mass cytometry, spectral flow cytometry and single-cell RNA sequencing, have considerably enhanced the resolution of immune phenotyping[159]. These technologies enable the detailed characterization of a broad spectrum of cell subsets and provide a highly granular insight into cell signalling pathways. Such advances pave the way for a more profound understanding of the immunopathogenesis of MG.

A complex issue arises when clinicians are confronted with multiple drugs that have the same mechanism of action. The selection process among these drugs can indeed be challenging, and guidelines for making informed decisions need to be established. Several key factors will influence the decision-making process, including the drug's safety profile, disease-modifying potential, steroid-sparing effect, onset time of treatment effects, therapy duration and patient compliance with the drug administration route. Importantly, complement inhibitors and FcRn inhibitors might have a role in the treatment of people with MG who are unable to undergo general immunosuppressive therapy owing to contraindications. Such individuals include people with cancer who have MG triggered by immune checkpoint inhibitors, as well as people with invasive thymoma and MG. Initial evidence suggests that eculizumab has potential for use in people with thymoma-associated MG[160] and as a rescue therapy in individuals experiencing MG crisis[161,162]. However, further studies are necessary to evaluate the efficacy of eculizumab specifically for these indications.

The identification of reliable biomarkers and the development of machine-learning algorithms that are capable of integrating data derived from multiomics and clinical phenotyping would provide useful insights to predict treatment outcomes and individualize therapies.

In addition, gaining comprehensive knowledge about the natural history of MG and establishing national and international registries will contribute substantially to our understanding of the disease. These initiatives will optimize therapeutic strategies by providing valuable knowledge about the effectiveness of different treatments and factors that influence patient outcomes. Furthermore, the development of personalized neuromuscular junction models using induced pluripotent stem cells derived from fibroblasts or peripheral blood mononuclear cells from people with MG offers promise for unravelling disease mechanisms and explaining the observed heterogeneity among people with the disease[163]. By studying patient-specific models, researchers will gain a deeper understanding of individual responses to therapies and tailor treatment approaches accordingly.

The molecular therapies discussed in this Review are poised to revolutionize the management of MG. However, many of these new treatments come with high financial burden. Comprehensive cost–effectiveness and cost–benefit analyses are urgently needed[164]. Variations in health-care systems among different countries can, importantly, have a considerable impact on the care provided to people with MG globally. Crucially, economic models must consider the long-term benefits of the new drugs. MG is a lifelong condition with potential life-threatening manifestations. New treatments have the potential to ameliorate childbearing prospects and professional trajectories for women. Furthermore, these therapeutic advances might enhance workplace attendance and efficiency among people with MG. This consideration is especially important given that many individuals are diagnosed with MG in the early stages of their life[165].

Given the emergence of new therapies, re-evaluation of the current clinical criteria used to assess the treatment response in MG is imperative. The absence of standardization in executing outcome measures represents a crucial factor contributing to the variability in clinical trial data. To address this issue, in 2023 a panel of experts recommended modifications that would enhance the application and reliability of these outcome measures[166]. Moreover, relying solely on reaching the minimal manifestation status, as defined by the Myasthenia Gravis Foundation of America Post-Interventional Status[167], might no longer be sufficient to assess treatment efficacy. Instead, a more comprehensive evaluation should be adopted, centred on the quality of life of people with MG, including the burden of drug-related adverse effects. Clinicians involved in the care of people with MG must collaborate to gather data and present evidence that facilitates the treatment decision-making process, with the goal of improving the quality of life of individuals with the disease. As advances in MG therapies continue to evolve, capturing not only the physician-reported and patient-reported outcomes, but also the overall well-being of affected individuals is essential. This broader approach to evaluating treatment response would provide a more holistic picture of the benefits and challenges associated with different therapeutic strategies.

Published online: 08 January 2024

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Competing interests

The author has received consultancy fees and speaker honoraria from Alexion, Argenx and UCB.

Additional information

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